

New Zealand Datasheet

Name of Medicine

PRADAXA[®]

Dabigatran etexilate

Presentation

75 mg hard capsules: Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 2 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with R75.

110 mg hard capsules: Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 1 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with R110.

150 mg hard capsules: Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 0 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with R150.

Uses

Actions

Pharmacotherapy group: oral direct thrombin inhibitor
ATC Code: B01AE07 - dabigatran etexilate

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma.

Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

In-vivo and ex-vivo animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of thrombosis.

There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect. Dabigatran prolongs the activated partial thromboplastin time (aPTT).

Pharmacokinetics

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with C_{max} attained within 0.5 and 2.0 hours post administration. C_{max} and the area under the plasma concentration-time curve were dose proportional. After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 11 hours in healthy elderly subjects. After multiple dose a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 1.

Table 1: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

| glomerular filtration rate (CrCl) | gMean (gCV%; range) half-life |
|--|--------------------------------------|
| [mL/min] | [h] |
| > 80 | 13.4 (25.7%; 11.0-21.6) |
| >50- ≤ 80 | 15.3 (42.7%;11.7-34.1) |
| > 30 - ≤ 50 | 18.4 (18.5%;13.3-23.0) |
| ≤ 30 | 27.2 (15.3%; 21.6-35.0) |

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 6.5 %.

Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours.

The oral bioavailability may be increased by 75% compared to the reference capsule formulation when the pellets are taken without the HPMC capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages) (see Dosage and Administration).

A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration, or at 7 to 9 hours following surgery (BISTRO Ib). It is noted however that contributing factors such as anaesthesia, gastrointestinal paresis, and surgical effects will mean that a proportion of patients will experience absorption delay independent of the oral drug formulation. Although this study did not predict whether impaired absorption persists with subsequent doses, it was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after drug administration.

Metabolism and excretion of dabigatran were studied following a single intravenous dose of radiolabelled dabigatran in healthy male subjects. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85%). Faecal excretion accounted for 6% of the administered dose. Recovery of the total radioactivity ranged from 88 - 94 % of the administered dose by 168 hours post dose.

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10% of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

Low (34-35%) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigatran of 60 – 70 L exceeded the volume of total body water indicating moderate tissue distribution of dabigatran.

Special populations

Renal impairment: The exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate in a phase I study was approximately 2.7 fold higher in volunteers with moderate renal insufficiency (CrCL between 30 - 50mL/min) than in those without renal insufficiency.

In a small number of volunteers with severe renal insufficiency (CrCL 10 - 30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see Dosage and Administration and Contraindications sections).

Elderly patients: Specific pharmacokinetic studies with elderly subjects in phase 1 studies showed an increase of 40 to 60% in the AUC and of more than 25 % in C_{max} compared to young subjects. The AUC_{τ,ss} and C_{max,ss} in male and female elderly subjects (> 65 y) were approximately 1.9 fold and 1.6-fold higher for elderly females compared to young females and 2.2 and 2.0 fold higher for elderly males than in male subjects of 18 - 40 years of age. The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance.

The effect by age on exposure to dabigatran was confirmed in the RE-LY study with an about 31 % higher trough concentration for subjects ≥ 75 years and by about 22 % lower trough level for subjects < 65 years compared to subjects of age between 65 and 75 years.

Hepatic insufficiency: No change in dabigatran exposure was seen in 12 subjects in a phase 1 study with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls.

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥ 2 Upper Limit Normal (ULN) were excluded in clinical trials.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.

Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥ 2 Upper Limit Normal (ULN), or hepatitis A, B or C were excluded in clinical trials.

Body weight: The dabigatran trough concentrations were about 20% lower in patients with a BW > 100 kg compared with 50 - 100 kg. The majority (80.8%) of the subjects were in the ≥ 50 kg and < 100 kg category with no clear difference detected. Limited data in patients ≤ 50 kg are available.

Gender: Drug exposure in the primary VTE prevention studies was about 40% to 50% higher in female patients. In atrial fibrillation patients females had on average 30 % higher trough and post-dose concentrations. This finding had no clinical relevance.

Ethnic origin: The pharmacokinetics of dabigatran was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the pharmacokinetics of dabigatran in a clinically relevant manner. Limited pharmacokinetic data in black patients are available which suggest no relevant differences.

Pharmacokinetic interactions: In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450. This has been confirmed by in vivo studies with healthy volunteers, who did not show any interaction between dabigatran treatment and the following drugs: atorvastatin (CYP3A4), digoxin (P-gp transporter interaction) and diclofenac (CYP2C9).

Atorvastatin: When dabigatran etexilate was coadministered with atorvastatin a CYP3A4 substrate, exposure of atorvastatin, atorvastatin metabolites and of dabigatran were unchanged indicating a lack of interaction.

NSAIDs

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

When dabigatran etexilate was coadministered with diclofenac, the plasma exposure of both medicinal products remained unchanged indicating a lack of a pharmacokinetic interaction between dabigatran etexilate and diclofenac. NSAIDs given for short-term perioperative analgesia for primary VTE prevention following major orthopedic surgery have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Due to the increased risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended (see section Warnings and Precautions).

P-gp inhibitor / inducer interactions

The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-glycoprotein (P-gp). Therefore co-medications with P-gp transporter inhibitors and inducers had been investigated.

Co-medication with P-gp inhibitors

Amiodarone: When dabigatran etexilate was coadministered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 60 % and 50 %, respectively.

Verapamil: When dabigatran etexilate was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased depending on timing of administration and formulation of verapamil.

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 180% and AUC by about 150%). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 90% and AUC by about 70%) or administration of multiple doses of verapamil (increase of C_{max} by about 60% and AUC by about 50%). This can be explained by the induction of P-gp in the gut by chronic verapamil treatment.

There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 10% and AUC by about 20%). This is explained by completed dabigatran absorption after 2 hours. (See Dosage and Administration).

No data are available for the parenteral application of verapamil; based on the mechanism of the interaction, no meaningful interaction is expected.

Ketoconazole: Ketoconazole increased total dabigatran AUC_{0-∞} and C_{max} values by 138 % and 135 %, respectively, after a single dose of 400 mg, and 153 % and 149 %, respectively, after multiple dosing of 400 mg ketoconazole qd.. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole.

Clarithromycin: When clarithromycin 500 mg twice daily was administered together with dabigatran etexilate no clinically relevant PK-interaction was observed (increased of C_{max} by about 19% and AUC by about 15%).

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1000 mg. Dabigatran etexilate was given bid over 3 consecutive days, on the 3rd day either with or without quinidine. Dabigatran AUC_{T,ss} and C_{max,ss} were increased on average by 53 % and 56 %, respectively with concomitant quinidine.

Co-medication with P-gp substrates

Digoxin: When dabigatran etexilate was coadministered with digoxin, a P-gp substrate, no PK-interaction was observed. Neither dabigatran nor the pro-drug dabigatran etexilate is a clinically relevant P-gp inhibitor.

Co-medication with P-gp inducers

Rifampicine: Pre-dosing of the probe inducer rifampicin at a dose of 600 mg qd for 7 days decreased total dabigatran peak and total exposure by 65.5 and 67 %, respectively. The inducing effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days.

Co-medications with platelet-inhibitors:

Acetylsalicylic acid (ASA): The effect of concomitant administration of dabigatran etexilate and acetylsalicylic acid (ASA) on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomized ASA coadministration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12 % to 18 % and 24% with 81 mg and 325 mg ASA, respectively. From the data gathered in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 or 150 mg bid may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was, however, also observed for warfarin.

NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate and this has not suggested additional bleeding risk.

Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. In addition, dabigatran AUC_{T,ss} and C_{max,ss} and the coagulation measures for dabigatran effect, aPTT, ECT or TT (anti FIIa), or the inhibition of platelet aggregation (IPA) as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 or 600 mg clopidogrel, dabigatran AUC_{T,ss} and C_{max,ss} were increased by about 30 to 40%.

Co-medication with gastric pH-elevating agents:

Pantoprazole: When dabigatran etexilate was coadministered with pantoprazole, a decrease in dabigatran area under the plasma concentration - time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors were co-administered with dabigatran etexilate in clinical trials and no effects on bleeding or efficacy were observed.

Ranitidine: Ranitidine administration together with dabigatran etexilate had no meaningful effect on the extent of absorption of dabigatran.

The changes in dabigatran exposure determined by population pharmacokinetic analysis caused by PPIs and antacids were not considered clinically relevant because the magnitude of the effect were minor (fractional decrease in bioavailability not significant for antacids and 14.6 % for PPIs).

In the phase III study, RE-LY, PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (- 11 %). Accordingly, PPI comedication seemed to be not associated with a higher incidence of stroke or SEE, especially in comparison with warfarin, and hence, the reduced bioavailability by pantoprazole co-administration seemed to be of no clinical relevance.

Indications

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.

Dosage and Administration

Dabigatran etexilate hard capsules should be taken with water, with or without food. Do not open the capsule.

Adults:

Prevention of Venous Thromboembolism (VTE) in patients following major orthopaedic surgery:

The recommended dose of dabigatran etexilate is 220 mg once daily taken as 2 capsules of 110 mg. Patients with moderate renal impairment have an increased risk for bleeding. For those patients the recommended dose of dabigatran etexilate is 150 mg once daily, taken as 2 capsules of 75 mg.

Treatment with dabigatran etexilate should be initiated orally within 1 – 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for the required duration. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

VTE prevention following knee replacement surgery:

Treatment with dabigatran etexilate should be initiated orally within 1 – 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 10 days. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

VTE prevention following hip replacement surgery:

Treatment with dabigatran etexilate should be initiated orally within 1 - 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 28 – 35 days. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

The recommended daily dose of Pradaxa is 300 mg taken orally as 150 mg hard capsules twice daily. Therapy should be continued life-long.

Children:

Dabigatran etexilate has not been investigated in patients <18 years of age. Treatment of children with dabigatran etexilate is not recommended.

Renal impairment:

There are no data to support use in patients with severe renal impairment (< 30 mL/min creatinine clearance); treatment in this population with dabigatran etexilate is not recommended.

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

Dosing should be reduced to 150 mg dabigatran etexilate taken once daily as 2 capsules of 75 mg in patients with moderate renal impairment (30-50 mL/min creatinine clearance).

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

No dose adjustment necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

Dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies.

Elderly:

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function. (see dosage and administration in renal impairment).

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

No dose adjustment necessary, patients should be treated with 220 mg dabigatran etexilate taken once daily as 2 capsules of 110 mg.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Patients aged 80 years and above should be treated with a daily dose of 220 mg taken orally as 110 mg hard capsules twice daily.

Weight:

No dose adjustment necessary.

Concomitant use of dabigatran etexilate with strong P-glycoprotein inhibitors e.g. amiodarone, quinidine or verapamil:

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

Dosing should be reduced to dabigatran etexilate 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive dabigatran etexilate and amiodarone, quinidine or verapamil (see Interactions).

Treatment initiation with verapamil should be avoided in patients following major orthopaedic surgery who are already treated with dabigatran etexilate. Simultaneous initiation of treatment with dabigatran etexilate and verapamil should also be avoided.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

No dose adjustment necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

Patients at risk of bleeding:

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.

Patients with an increased bleeding risk (see Warnings and Precautions) should be closely clinically monitored (looking for signs of bleeding or anaemia). A coagulation test (see section warnings and precautions), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. In such patients a dose of 220 mg given as 110 mg twice daily may be considered.

Switching from dabigatran etexilate treatment to parenteral anticoagulant:

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

Wait 24 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Wait 12 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to dabigatran etexilate:

Dabigatran etexilate should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous UFH).

Switching from Vitamin K antagonists to dabigatran etexilate:

The Vitamin K antagonist should be stopped. Dabigatran etexilate can be given as soon as the INR is < 2.0.

Switching from dabigatran etexilate to Vitamin K antagonists:

When converting from dabigatran etexilate to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For CrCl >50 mL/min, start warfarin 3 days before discontinuing dabigatran etexilate.
- For CrCl 31-50 mL/min, start warfarin 2 days before discontinuing dabigatran etexilate.
- For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing dabigatran etexilate.
- For CrCl <15 mL/min, no recommendations can be made.

Cardioversion

Patients can stay on dabigatran etexilate while being cardioverted.

Missed dose

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

Continue with your remaining daily doses of dabigatran etexilate at the same time of the next day. Do not take a double dose to make up for missed individual doses.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted. Do not take a double dose to make up for missed individual doses.

Contraindications

- Known hypersensitivity to dabigatran or dabigatran etexilate or to one of the excipients of the product
- Severe renal impairment (CrCl < 30mL/min)
- Haemorrhagic manifestations, patients with a bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis
- Organ lesions at risk of clinically significant bleeding, including haemorrhagic stroke within the last 6 months
- Indwelling spinal or epidural catheter and during the first hour after removal (see Warnings and Precautions).
- Concomitant treatment with systemic ketoconazole (see Interactions)

Warnings and Precautions

Haemorrhagic risk

As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with dabigatran. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site.

Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors are combined.

The following table summarises factors which may increase the haemorrhagic risk as identified in clinical studies.

| | |
|---|--|
| Factors increasing dabigatran plasma levels | <ul style="list-style-type: none"> • Moderate renal impairment (30-50 ml/min CrCl) • P-glycoprotein-inhibitor co-medication |
| Pharmacodynamic interactions | <ul style="list-style-type: none"> • Acetylsalicylic acid • NSAID • Clopidogrel |
| Diseases / procedures with special haemorrhagic risks | <ul style="list-style-type: none"> • Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Active ulcerative gastrointestinal disease • Recent gastrointestinal bleeding • Recent biopsy or major trauma • Recent intracranial haemorrhage • Brain, spinal or ophthalmic surgery • Bacterial endocarditis |
| Others | <ul style="list-style-type: none"> • Age ≥ 75 years |

The measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran.

In patients who are bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT > 80 sec at trough (when the next dose is due) is associated with a higher risk of bleeding.

Patients who develop acute renal failure must discontinue Pradaxa.

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding, the aPTT test maybe useful to

assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT greater than 80 sec is associated with a higher risk of bleeding.

Pharmacokinetic studies demonstrated an increase in drug exposure in patients with reduced renal function including age-related decline of renal function. Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCL < 30 ml/min).

Hepatic impairment:

Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials investigating the VTE prevention following elective hip or knee replacement surgery as well as in RE-LY study investigating the prevention of stroke and systemic emboli associated with atrial fibrillation. No treatment experience is available for this subpopulation of patients, and therefore the use of Pradaxa is not recommended in this population (see Pharmacokinetics).

Patients who develop acute renal failure should discontinue dabigatran etexilate.

Factors, such as decreased renal function (30 - 50ml/min CrCL), age ≥ 75 years, or strong P-gp-inhibitor comedication are associated with increased dabigatran plasma levels. The presence of one or more than one of these factors may increase the risk of bleeding (see Dosage and Administration).

The concomitant use of Pradaxa with the following treatments has not been studied and may increase the risk of bleeding: unfractionated heparins (except at doses necessary to maintain patency of central venous or arterial catheter) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfapyrazone, rivaroxaban, prasugrel, vitamin K antagonists, and the P-gp inhibitors dronedarone, itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.

In situations where there is an increased haemorrhagic risk (e.g. recent biopsy or major trauma, bacterial endocarditis) close observation (looking for signs of bleeding or anaemia) is generally required.

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate and this has not suggested additional bleeding risk.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Co-administration of oral anti-platelet (including aspirin and clopidogrel) and NSAID therapies increase the risk of bleeding.

Interaction with P-gp inducers:

The concomitant use of dabigatran etexilate with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John`s Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution (see interaction and special population).

Surgery and Interventions:

Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate.

Preoperative Phase

In advance of invasive or surgical procedures dabigatran etexilate should be stopped temporarily due to an increased risk of bleeding. If possible, dabigatran etexilate should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete hemostasis may be required consider stopping dabigatran etexilate 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures.

Dabigatran etexilate is contraindicated in patients with severe renal dysfunction (CrCl <30 mL/min) but should this occur then dabigatran etexilate should be stopped at least 5 days before major surgery.

If an acute intervention is required, dabigatran etexilate should be temporarily discontinued. A surgery / intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed there may be an increase in the risk of bleeding. This risk of bleeding should be weighed together with the urgency of intervention.

Spinal Anesthesia/Epidural Anesthesia/Lumbar Puncture

Procedures such as spinal anesthesia may require complete hemostatic function.

The risk of spinal or epidural hematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 1 hour should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma.

Post Procedural Period

Resume treatment after complete haemostasis is achieved.

The product contains the excipient sunset yellow, which may cause allergic reactions.

Effects on Fertility

In the fertility study in rats, no toxicologically remarkable parental findings were noted. With respect to litter parameters, a slight decrease in corpora lutea and an increase in pre-implantation loss led to a decrease in the mean number of implantations in the 200 mg/kg (free base equivalent) dose group.

Use in Pregnancy

No clinical data on exposed pregnancies are available. The potential risk for humans is unknown.

Teratology studies were performed with up to 200 mg/kg (free base equivalent) in rats and rabbits. A slight effect on the morphogenesis of foetuses was observed in rats at 200 mg/kg (free base equivalent). No teratogenic effects were noted in rabbits.

Women of child-bearing potential should avoid pregnancy during treatment with dabigatran etexilate and when pregnant, women should not be treated with dabigatran etexilate unless the expected benefit is greater than the risk.

Use in Lactation

No clinical data are available. As a precaution, breast-feeding should be stopped.

Effect on Fertility

No data available

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

Paediatric use

There is no experience in children. Dabigatran etexilate has not been investigated in patients <18 years of age. Treatment of children with dabigatran etexilate is not recommended.

Use in the elderly

The clinical studies have been conducted in a patient population with a mean age > 65 years. In general, patients should be treated with the standard dose of 220 mg dabigatran etexilate daily. Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function (see Precautions, Renal Insufficiency section)

Carcinogenicity

The tumorigenic potential of dabigatran etexilate is currently being investigated in rats and mice at maximum doses of 200 mg/kg (free base equivalent).

Genotoxicity

Comprehensive in vitro- and in vivo studies revealed no evidence of a mutagenic potential.

Adverse Effects

The safety of dabigatran etexilate has been evaluated overall in 22,687 patients.

In the primary VTE prevention trials after major orthopaedic surgery a total of 10,596 patients were treated in 5 controlled studies with at least one dose of study medication. Of these 5,674 were treated with 150 or 220 mg once daily of dabigatran etexilate, while 522 received doses less than 150 mg once daily and 1168 received doses in excess of 220 mg once daily.

In the RE-LY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation a total of 12,091 patients were randomized. Of these 6,076 were treated with 150 mg twice daily of dabigatran etexilate, while 6,015 received doses of 110 mg twice daily.

In total, about 9 % of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days) and 22 % of patient with atrial fibrillation treated for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years) experienced adverse reactions.

Bleeding

Bleeding is the most relevant side effect of dabigatran etexilate; dependant of the indication bleeding of any type or severity occurred in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery and in long-term treatment in yearly 16.5 % of patient with atrial fibrillation treated for the prevention of stroke and systemic embolism.

Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

Overall bleeding rates were similar between treatment groups and not significantly different.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Major bleeding fulfilled one or more of the following criteria:

- Bleeding associated with a reduction in hemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells;
- Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding.

Major bleeds were classified as life-threatening if they fulfilled one or more of the following criteria:

- Fatal bleed; symptomatic intracranial bleed; reduction in hemoglobin of at least 50 grams per liter; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

Subjects randomized to dabigatran etexilate 110 mg twice daily and 150mg twice daily had a significantly lower risk for life-threatening bleeds, haemorrhagic stroke and intracranial bleeding compared to warfarin ($p < 0.05$). Both dose strengths of dabigatran etexilate had also a statistically significant lower total bleed rate. Subjects randomized to dabigatran etexilate 110mg twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.79, $p = 0.0021$)

Table 2: Bleeding events broken down to major and any bleeding in the pivotal study testing the prevention of thromboembolic SSE in patients with atrial fibrillation.

| | Dabigatran etexilate 110 mg twice daily | Dabigatran etexilate 150 mg twice daily | Warfarin |
|---------------------------|--|--|-----------------|
| Subjects randomized | 6,015 | 6,076 | 6,022 |
| Major Bleeding | 342 (2.87 %) | 399 (3.32 %) | 421 (3.57 %) |
| Intracranial bleeding | 27 (0.23 %) | 38 (0.32 %) | 90 (0.76 %) |
| Gastrointestinal bleeding | 134 (1.14 %) | 186 (1.57 %) | 125 (1.07 %) |
| Fatal bleeding | 23 (0.19 %) | 28 (0.23 %) | 39 (0.33 %) |
| Minor bleeding | 1,566 (13.16 %) | 1,787 (14.85%) | 1,931 (16.37%) |
| Any bleeding | 1,754 (14.74 %) | 1,993 (16.56 %) | 2,166 (18.37 %) |

Side effects:

Adverse reactions classified by SOC and MedDRA preferred terms reported from any treatment group per population of all controlled studies are shown in the listings below. Table 3 lists identified side effects applicable to both indications. Table 4 lists indication specific side effects identified.

Side effects are generally associated to the pharmacological mode of action of dabigatran etexilate and represent bleeding associated events that may occur in different anatomical regions and organs.

In patients treated for VTE prevention after hip or knee replacement surgery the observed incidences of side effects of dabigatran etexilate were in the range of enoxaparin.

The observed incidences of side effects of dabigatran etexilate in patients treated for stroke prevention after atrial fibrillation were in the range of warfarin except gastrointestinal disorders which appeared at a higher rate in the dabigatran etexilate arms.

Table 3: Side effects identified from the *Primary VTE prevention studies after major orthopaedic surgery program* and the *Prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation at moderate to high risk of stroke program*.

| |
|--|
| <u>Blood and lymphatic system disorders</u> |
| Anaemia, Thrombocytopenia |
| |
| <u>Immune system disorders</u> |
| Drug hypersensitivity including urticaria, rash and pruritus, bronchospasm |
| |
| <u>Nervous system disorders</u> |
| Intracranial haemorrhage |
| |

| |
|---|
| <u>Vascular disorders</u> |
| Haematoma, Haemorrhage |
| |
| <u>Respiratory, thoracic and mediastinal disorders</u> |
| Epistaxis, haemoptysis |
| |
| <u>Gastrointestinal disorders</u> |
| Gastrointestinal haemorrhage, Abdominal pain, diarrhoea, dyspepsia, nausea, gastrointestinal ulcer, gastroesophagitis, gastroesophageal reflux disease, vomiting, dysphagia |
| |
| <u>Hepatobiliary disorders</u> |
| Hepatic function abnormal |
| |
| <u>Skin and subcutaneous tissue disorders</u> |
| Skin haemorrhage |
| |
| <u>Musculoskeletal, connective tissue and bone disorders</u> |
| Haemarthrosis |
| |
| <u>Renal and urinary disorders</u> |
| Urogenital haemorrhage, Haematuria |
| |
| <u>General disorders and administration site conditions</u> |
| Injection site haemorrhage, Catheter site haemorrhage |
| |
| <u>Injury, poisoning and procedural complications</u> |
| Traumatic haematoma, Incision site haemorrhage |

Table 4: Additional specific side effects identified per indication

| |
|---|
| <i>Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.</i> |
| |
| <u>Vascular disorders</u> |
| Wound haemorrhage |
| |
| <u>General disorders and administration site conditions</u> |
| Bloody discharge |
| |
| <u>Injury, poisoning and procedural complications</u> |
| Post-procedural haematoma, Post-procedural haemorrhage, Anaemia post-operative, Post-procedural discharge, Wound secretion, |
| |
| <u>Surgical and medical procedures</u> |
| Wound drainage, Post-procedural drainage, |
| |
| <i>Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:</i> |
| |
| None |

Interactions

The concomitant use of dabigatran etexilate with treatments that act on haemostasis or coagulation including Vitamin K antagonists can markedly increase the risk of bleeding.

Anticoagulants and platelet aggregation agents:

The following treatments should not be administered concomitantly with dabigatran etexilate: unfractionated heparins and heparin derivatives low molecular weight heparins (LMWH), except for bridging situations when switching from dabigatran etexilate treatment to parenteral anticoagulant or vice versa, factor Xa inhibitors like fondaparinux, other thrombin inhibitors like desirudin, thrombolytic agents, GpIIb/IIIa receptor antagonists, anti-thrombotic agents like ticlopidine, dextran, sulfapyrazone and vitamin K antagonists except for converting patients from dabigatran etexilate to vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter.

From the data collected in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 mg or 150 mg twice daily may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin.

The co-administration of low-dose aspirin and / or clopidogrel with dabigatran etexilate should be accompanied by clinical observation for bleeding.

P-gp interactions:

P-glycoprotein inhibitors:

Amiodarone: Dabigatran exposure in healthy subjects was increased by 60 % in the presence of amiodarone (see Pharmacokinetics - special populations).

Verapamil: When dabigatran etexilate (150 mg) was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased but magnitude of this change differs depending on timing of administration and formulation of verapamil (see Pharmacokinetics - special populations).

Quinidine: Dabigatran exposure in healthy subjects was increased by 53 % in the presence of quinidine (see Pharmacokinetics - special populations).

Clarithromycin:

Dabigatran exposure in healthy subjects was increased by 15 % in the presence of clarithromycin without any clinical safety concern (see Pharmacokinetics - special populations).

Ketoconazole:

Dabigatran exposure was 150 % increased after single and multiple doses of Ketoconazole (see Contraindications and Pharmacokinetics - special populations).

P-glycoprotein substrate:

Digoxin: In a study performed with 24 healthy subjects, when Pradaxa was coadministered with digoxin, no changes on digoxin and no clinical relevant changes on dabigatran exposure have been observed (see Pharmacokinetics - special populations).

P-glycoprotein inducers:

After 7 days of treatment with 600 mg rifampicin qd total dabigatran AUC_{0-∞} and C_{max} were reduced by 67% and 66% compared to the reference treatment, respectively. Caution should be exercised with strong P-glycoprotein inducers (see Warnings and Precautions and Pharmacokinetics - special population).

Overdosage

Overdose following administration of dabigatran etexilate may lead to haemorrhagic complications due to its pharmacodynamic properties. A specific antidote antagonising the pharmacodynamic

effect of dabigatran etexilate is not available. Doses of dabigatran etexilate beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of dabigatran etexilate. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Appropriate standard treatment, e.g., surgical haemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or fresh frozen plasma. As protein binding is low, dabigatran is dialysable, however there is limited clinical experience in using dialysis in this setting [2].

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX or X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.

Pharmaceutical Precautions

CAPSULES (blister packs): Store below 30°C. Protect from moisture.

CAPSULES (bottle): Store below 30°C. Protect from moisture. Once opened, the bottle must be used within 30 days. Keep the bottle tightly closed.

Medicine Classification

Prescription Medicine

Package Quantities

Capsules 75 mg: Blister packs: 10, 30, 60 capsules.
Bottle: 60 capsules.

Capsules 110mg : Blister packs: 10, 30, 60 capsules.
Bottle: 60 capsules.

Capsules 150mg : Blister packs: 10, 30, 60 capsules.
Bottle: 60 capsules.

Not all pack sizes may be marketed.

Further Information

PRADAXA[®] is a registered Trademark

Excipients

Capsule fill: Tartaric acid, acacia, hypromellose, dimethicone 350, talc, hydroxypropylcellulose
HPMC capsule shell: Sodium carragenan, potassium chloride, titanium dioxide, sunset yellow FCF (E110), indigo carmine (E132), hypromellose, water - purified
Printing ink: Shellac, tert-butyl alcohol, isopropyl alcohol, methylated spirit - industrial, iron oxide black (E172), water - purified, propylene glycol.

Clinical Trials

Clinical trials in primary VTE prevention following major joint replacement surgery:

In 2 large randomised, parallel group, double-blind, dose–confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received dabigatran etexilate 75 mg or 110 mg within 1-4 hours of surgery followed by 150 or 220 mg once daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and once daily thereafter.

In the RE-MODEL trial (knee replacement) treatment was for 6 – 10 days and in the RE-NOVATE trial (hip replacement) for 28 – 35 days. Totals of 2076 patients (knee) and 3494 (hip) were treated respectively.

The results of the knee study (RE-MODEL) with respect to the primary end-point, total venous thromboembolism (VTE) including asymptomatic venous (VTE) plus all-cause mortality showed that the antithrombotic effect of both doses of dabigatran etexilate were statistically non-inferior to that of enoxaparin.

Similarly, total VTE including asymptomatic VTE and all-cause mortality constituted the primary end-point for the hip study (RE-NOVATE). Again dabigatran etexilate at both once daily doses was statistically non-inferior to enoxaparin 40 mg daily.

Furthermore in a third randomized, parallel group, double-blind, trial (RE-MOBILIZE), patients undergoing elective total knee surgery received dabigatran etexilate 75 mg or 110 mg within 6-12 hours of surgery followed by 150 mg and 220 mg once daily thereafter. The treatment duration was 12-15 days. In total 2615 patients were randomised and 2596 were treated. The comparator dosage of enoxaparin was 30 mg twice daily according to the US label. In the RE-MOBILIZE trial non–inferiority was not established. There were no statistical differences in bleeding between the comparators.

In addition a randomized, parallel group, double-blind, placebo-controlled phase II study in Japanese patients where dabigatran etexilate 110 mg, 150 mg, and 220 mg was administered at the next day after elective total knee replacement surgery was evaluated. The Japanese study showed a clear dose response relationship for the efficacy of dabigatran etexilate and a placebo like bleeding profile.

In RE-MODEL and RENOVATE the randomisation to the respective study medication was done pre-surgery, and in the RE-MOBILIZE and the Japanese placebo controlled trial the randomisation to the respective study medication was done post-surgery. This is of note especially in the safety evaluation of these trials. For this reason the trials are grouped in pre- and post surgery randomised trials in the previous Table 1 above.

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in table 5 below. VTE was defined as the composite incidence of deep vein thrombosis and Pulmonary Embolism.

Table 5 - Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies

| Trial | Dabigatran etexilate 220 mg | Dabigatran etexilate 150 mg | Enoxaparin 40 mg |
|---|--------------------------------|--------------------------------|---------------------|
| RE-NOVATE (hip) | | | |
| N | 909 | 888 | 917 |
| Incidences (%) | 28 (3.1) | 38 (4.3) | 36 (3.9) |
| Risk differences vs. enoxaparin (%) | - 0.8 | 0.4 | |
| 95 % CI | - 2.5, 0.8 | - 1.5, 2.2 | |
| Risk ratio over enoxaparin | 0.78 | 1.09 | |
| 95% CI | 0.48, 1.27 | 0.70, 1.70 | |
| RE-MODEL (knee) | | | |
| N | 506 | 527 | 511 |
| Incidences (%) | 13 (2.6) | 20 (3.8) | 18 (3.5) |
| Risk differences vs. enoxaparin (%) | - 1.0 | 0.3 | |
| 95 % CI | - 3.1, 1.2 | -2.0, 2.6 | |
| Risk ratio over enoxaparin | 0.73 | 1.08 | |
| 95% CI | 0.36, 1.47 | 0.58, 2.01 | |
| RE-MOBILIZE (knee) ² | | | Enoxaparin 60 mg |
| N | 618 | 656 | 668 |
| Incidences (%) | 21 (3.4) | 20 (3.0) | 15 (2.2) |
| Risk differences vs. enoxaparin (%) | 1.2 | 0.8 | |
| 95 % CI | (-0.7, 3.0) | (-0.9, 2.5) | |
| Risk ratio over enoxaparin | 1.51 | 1.36 | |
| 95% CI | (0.79, 2.91) | (0.70, 2.63) | |
| Japanese knee study ² | | | |
| | | | Placebo |
| N | 102 | 113 | 104 |
| Incidences (%) | 0 | 2 (1.8) | 6 (5.8) |
| Risk differences vs. placebo (%) | -5.8 | -4.0 | |
| 95 % CI | (-10.3, -1.3) | (-9.1, 1.1) | |
| ¹ pre-operative randomisation studies | | | |
| ² post-operative randomisation studies | | | |

Clinical trials in prevention of stroke and systemic embolism in patients with atrial fibrillation:

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomized Evaluation of Long –term anticoagulant therapy) a multi-center, multi-national, randomized parallel group study of two blinded doses of dabigatran (110 mg bid and 150 mg bid) compared to open-label warfarin in patients with atrial fibrillation at moderate to high risk of stroke or systemic embolism. The primary objective in this study was to determine if dabigatran was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke and systemic embolic events (SEE).

In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean CHADS₂ score of 2.1. The population had approximately equal proportions of

patients with CHADS₂ score 1, 2 and ≥ 3. The patient population was 64% male, 70% Caucasian and 16% Asian. RE-LY had a median treatment of 20 months with dabigatran etexilate given as fixed dose without coagulation monitoring. In addition to documented non-valvular atrial fibrillation (AF) e.g., persistent AF or paroxysmal, patients had one of the following additional risk factors for stroke:

- Previous stroke, transient ischemic attack, or systemic embolism
- Left ventricular ejection fraction <40 %
- Symptomatic heart failure, ≥ NYHA Class 2
- Age ≥ 75 years
- Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and CAD 28%. 50% of the patient population was VKA naïve defined as less than 2 months total life time exposure. 32% of the population had never been exposed to a VKA. For those patients randomized to warfarin, the time in therapeutic range (INR 2 to 3) for the trial was a median of 67%. Concomitant medications included aspirin (25% of subjects used at least 50% of the time in study), clopidogrel (3.6%), ASA+clopidogrel (2%), NSAIDs (6.3%), beta-blockers (63.4%), diuretics (53.9%), statins (46.4%), ACE-inhibitors (44.6%), angiotensin receptor blockers (26.1%), oral hypoglycemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%), and proton pump inhibitors (17.8%).

For the primary endpoint, stroke and systemic embolism, no subgroups (i.e., age, weight, gender, renal function, ethnicity, etc.) were identified with a different risk ratio compared to warfarin.

This study demonstrated that dabigatran etexilate, at a dose of 110 mg twice daily, is non-inferior to warfarin in the prevention of stroke and systemic embolism in subjects with atrial fibrillation, with a reduced risk of intracranial hemorrhage and total bleeding. The higher dose of 150 mg twice daily, reduces significantly the risk of ischemic and hemorrhagic stroke, vascular death, intracranial hemorrhage and total bleeding compared to warfarin. The lower dose of dabigatran has a significantly lower risk of major bleeding compared to warfarin.

Figure 1 and tables 6 - 10 display details of key results:

Table 6: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in the RE-LY

| | Dabigatran etexilate 150 mg bid | Dabigatran etexilate 110 mg bid | Warfarin |
|-------------------------------------|------------------------------------|------------------------------------|------------|
| Subjects randomized | 6076 | 6015 | 6022 |
| Stroke and/or SEE | | | |
| Incidences (%) | 134 (1.11) | 183 (1.54) | 202 (1.71) |
| Hazard ratio over warfarin (95% CI) | 0.65 (0.52, 0.81) | 0.90 (0.74, 1.10) | |
| p value superiority | p < 0.0001 | p = 0.2943 | |

% refers to yearly event rate

Figure 1: Kaplan-Mayer curve estimate of time to first stroke or systemic embolism

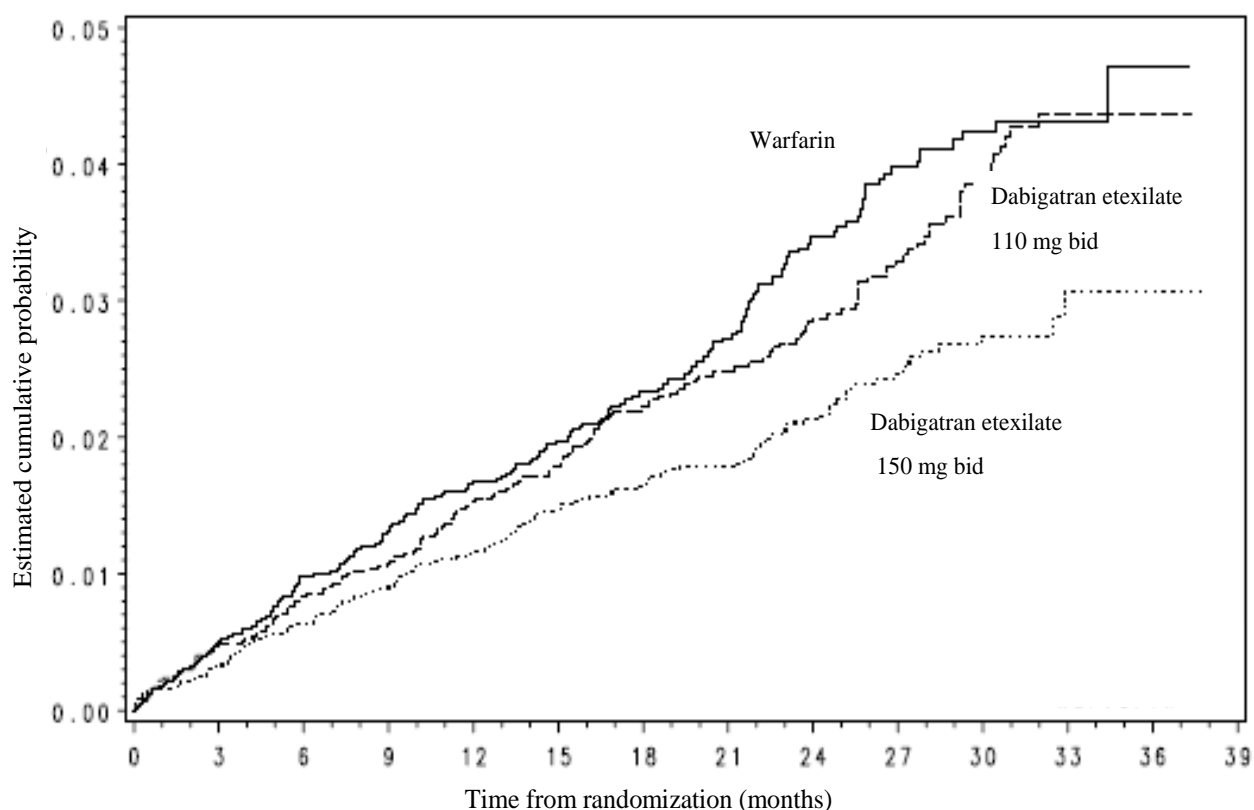


Table 7: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in the RE-LY

| | Dabigatran etexilate 150 mg bid | Dabigatran etexilate 110 mg bid | Warfarin |
|------------------------------------|------------------------------------|------------------------------------|------------|
| Subjects randomized | 6076 | 6015 | 6022 |
| Stroke | | | |
| Incidences (%) | 122 (1.01) | 171 (1.44) | 186 (1.58) |
| Hazard ratio vs. warfarin (95% CI) | 0.64 (0.51, 0.81) | 0.91 (0.74, 1.12) | |
| p-value | <0.0001 | 0.3828 | |
| SEE | | | |
| Incidences (%) | 13 (0.11) | 15 (0.13) | 21 (0.18) |
| Hazard ratio vs. warfarin (95% CI) | 0.61 (0.30, 1.21) | 0.71 (0.37, 1.38) | |
| p-value | 0.1582 | 0.3099 | |
| Ischemic stroke | | | |
| Incidences (%) | 103 (0.86) | 152 (1.28) | 134 (1.14) |
| Hazard ratio vs. warfarin (95% CI) | 0.75 (0.58, 0.97) | 1.13 (0.89, 1.42) | |
| p-value | 0.0296 | 0.3139 | |
| Hemorrhagic stroke | | | |
| Incidences (%) | 12 (0.10) | 14 (0.12) | 45 (0.38) |
| Hazard ratio vs. warfarin (95% CI) | 0.26 (0.14, 0.49) | 0.31 (0.17, 0.56) | |
| p-value | <0.001 | <0.001 | |

% refers to yearly event rate

Table 8: Analysis of all cause and cardiovascular survival during the study period in the RE-LY

| | Dabigatran etexilate 150 mg bid | Dabigatran etexilate 110 mg bid | Warfarin |
|---------------------------------------|------------------------------------|------------------------------------|------------|
| Subjects randomized | 6076 | 6015 | 6022 |
| All-cause mortality | | | |
| Incidences (%) | 438 (3.64) | 446 (3.75) | 487 (4.13) |
| Hazard ratio vs. warfarin (95% CI) | 0.88 (0.77, 1.00) | 0.91 (0.80, 1.03) | |
| p-value | 0.0517 | 0.1308 | |
| Vascular mortality | | | |
| Incidences (%) | 274 (2.28) | 289 (2.43) | 317 (2.69) |
| Hazard ratio vs. warfarin (95% CI) | 0.85 (0.72, 0.99) | 0.90 (0.77, 1.06) | |
| p-value | 0.0430 | 0.2081 | |

% refers to yearly event rate

The net clinical benefit (NCB) as measured by the unweighted composite clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, vascular deaths, and major bleeds was assessed and is presented as part of Table 9. The yearly event rates for the dabigatran etexilate groups were lower compared to the warfarin group. The risk reduction for this composite endpoint was 8% and 10% for the dabigatran etexilate 110 mg bid and 150 mg bid treatment groups. Other components evaluated included all hospitalizations which had statistically significant fewer hospitalizations at dabigatran etexilate 110 mg bid compared to warfarin (7% risk reduction, 95% CI 0.87, 0.99, p=0.021).

Table 9: Other Measures Evaluated

| | Dabigatran etexilate 150 mg bid | Dabigatran etexilate 110 mg bid | Warfarin |
|---|------------------------------------|------------------------------------|------------|
| Subjects randomized | 6076 | 6015 | 6022 |
| Stroke/SEE/death | | | |
| Incidences (%) | 520 (4.32) | 577 (4.85) | 613 (5.20) |
| Hazard ratio vs. warfarin (95%CI) | 0.83 (0.74, 0.93) | 0.93 (0.83, 1.045) | |
| p-value | 0.0015 | 0.2206 | |
| Stroke/SEE/PE/MI/death/maj or bleed (net clinical benefit) | | | |
| Incidences (%) | 848 (7.05) | 863 (7.25) | 925 (7.84) |
| Hazard ratio vs. Warfarin (95%CI) | 0.90 (0.82, 0.99) | 0.92 (0.84, 1.01) | |
| p-value | 0.0254 | 0.0852 | |
| Pulmonary embolism | | | |
| Incidences (%) | 18 (0.15) | 14 (0.12) | 12 (0.10) |
| Hazard ratio vs. Warfarin (95%CI) | 1.41 (0.71, 3.06) | 1.16 (0.54, 2.51) | |
| p-value | 0.2980 | 0.7076 | |
| Myocardial infarction | | | |
| Incidences (%) | 97 (0.81) | 98 (0.82) | 75 (0.64) |
| Hazard ratio vs. Warfarin (95%CI) | 1.27 (0.94, 1.71) | 1.29 (0.96, 1.75) | |
| p-value | 0.1240 | 0.0929 | |

Table 10 Liver Function Tests

In the RE-LY study, potential abnormalities of liver function tests (LFT) occurred with a comparable or lower incidence in dabigatran etexilate vs. warfarin treated patients

| | Dabigatran etexilate 150 mg bid N (%) | Dabigatran etexilate 110 mg bid N (%) | Warfarin N (%) |
|--|---|---|-------------------|
| Total treated | 6059 (100.0) | 5983 (100.0) | 5998 (100.0) |
| ALT or AST > 3xULN | 106 (1.7) | 118 (2.0) | 125 (2.1) |
| ALT or AST > 5xULN | 45 (0.7) | 36 (0.6) | 50 (0.8) |
| ALT or AST > 3xULN + Bilirubin >2xULN | 14 (0.2) | 11 (0.2) | 21 (0.4) |

Pre-clinical Toxicology

Acute oral toxicity studies were conducted in rats and mice. In both species, the approximate lethal dose after single oral administration was above 2000 mg/kg. In dogs and Rhesus monkeys, oral administration of 600 mg/kg dabigatran etexilate did not induce any toxicologically meaningful changes.

In repeat-dose toxicity studies over a maximum of 26 weeks in rats and 52 weeks in Rhesus monkeys, dosages up to 300 mg/kg (free base equivalent) were used. Generally, these doses were tolerated remarkably well by both, rats and Rhesus monkeys. Bleeding problems were observed in association with traumata (e.g. blood sampling) within the first 4 – 6 hours after administration and are directly related to the pharmacodynamic activity of dabigatran.

Teratology studies were performed with up to 200 mg/kg (free base equivalent) in rats and rabbits. A slight effect on the morphogenesis of foetuses was observed in rats at 200 mg/kg (free base equivalent). No teratogenic effects were noted in rabbits.

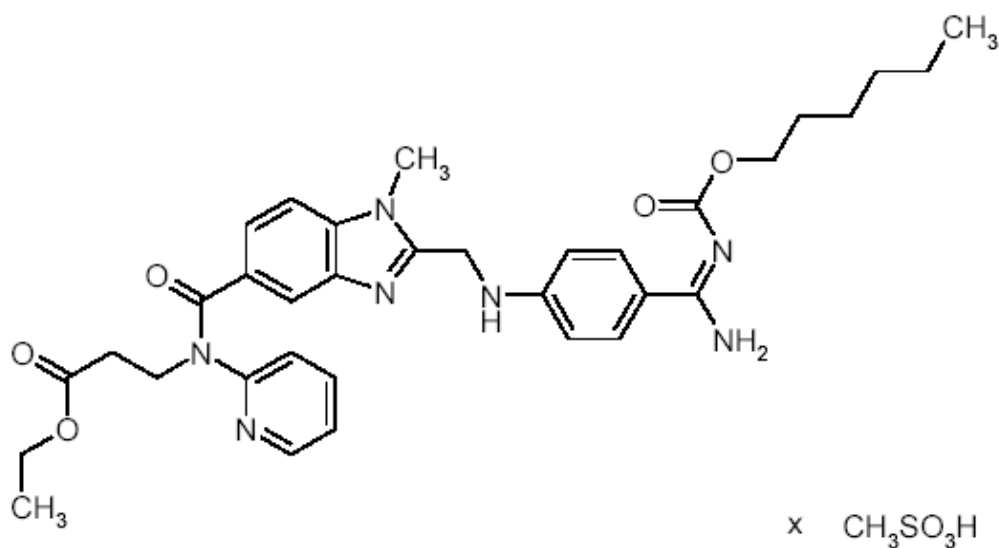
In the fertility study in rats, no toxicologically remarkable parental findings were noted. With respect to litter parameters, a slight decrease in corpora lutea and an increase in pre-implantation loss led to a decrease in the mean number of implantations in the 200 mg/kg (free base equivalent) dose group.

Comprehensive in vitro- and in vivo-studies revealed no evidence of a mutagenic potential.

In lifetime toxicology studies in rats and mice, there was no evidence for a tumorigenic potential of dabigatran up to maximum doses of 200 mg/kg (free base equivalent).

Chemical Structure

Dabigatran etexilate is beta-Alanine, N-[[2-[[[4(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methane-sulfonate.



Molecular Formula: C₃₅H₄₅N₇O₈S

CAS Registry Number: 211915-06-9 (free base)
593282-20-3 (mesilate)

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